Effects of Maternal Age and Cohort of Birth on Incidence Time Trends of Childhood Acute Lymphoblastic Leukemia

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Abstract

Several studies report increasing trends in the incidence of childhood acute lymphoblastic leukemia (ALL). Because ALL may generate *in utero*, this study investigated if maternal age and birth cohort influence ALL temporal trends. Data on 252 ALL cases in children ages 1 to 5 years were extracted from the population-based Childhood Cancer Registry of Piedmont, Italy. Information on cases' maternal age and year of birth was obtained from the registry, whereas population data were obtained for children born in 1980 to 1997. Incidence rates were analyzed using an age-period-cohort approach, in which the period effect was represented by the child year of birth, the age effect by the maternal age at the time of delivery, and the cohort effect by the maternal birth cohort. ALL incidence increased over the study period [annual percentage change 2.49%; 95% confidence interval (95% CI), 0.09-4.93]. A linear effect of the maternal time variables ($P = 0.012$) was found, which was equally described by maternal age (direct association) and maternal birth cohort (inverse association). The annual percentage change was 1.83% (95% CI, −0.59-4.31), when maternal age was included in the model, and 5.72% (95% CI, 2.29-9.27), when maternal year of birth was included. In conclusion, maternal characteristics substantially affect temporal trends in childhood ALL incidence. (Cancer Epidemiol Biomarkers Prev 2007;16(2):347–51)

Introduction

Childhood cancer incidence has been increasing for decades in Europe for unknown reasons (1). This trend is stronger among the youngest age groups (<5 years), in which acute lymphoblastic leukemia (ALL) is the most common type of tumor (1).

Environmental factors acting prenatally are suggestive candidate risk factors for tumors occurring among the youngest children. In the last decade, several specific chromosomal translocations associated with ALL have been found to be present already at birth, strongly supporting the hypothesis that childhood ALL may generate during the fetal period (2-8). Perinatal factors, including large birth weight (9, 10), parental education, and occupation (11), have been analyzed in several studies and linked with the risk of childhood ALL.

Results on maternal age are much more inconsistent. Notably, cohort studies tend to find an effect of older maternal age (12-15), whereas case-control studies are more conflicting and generally reveal weaker, if any, effects (10, 16-33). Elucidation of the actual role of maternal age is needed before attempting to understand the possible underlying biological mechanisms. Maternal age has been increasing over time in many populations, and such a trend might have modulated the increasing trends in childhood cancer incidence. Maternal age is perfectly collinear with the maternal birth cohort, after controlling on birth cohort of the child. Although the effect of the maternal cohort of birth has not been investigated in childhood cancer etiology, it is reasonable to assume that this variable affects temporal trends in ALL incidence if maternal lifestyle during pregnancy, such as smoking and diet that partly depends on the cohort of birth, are risk factors for ALL.

To investigate the effects of maternal age and maternal year of birth on temporal trends in incidence of childhood ALL occurring at ages 1 to 5 years (i.e., the age group with the highest incidence rates of ALL), we analyzed data from the Childhood Cancer Registry of Piedmont (CCRP), Italy, through an age-period-cohort approach.

Materials and Methods

Cancer and Population Data. Data on incident cases of childhood tumors were extracted from the CCRP, northwest Italy. This is a population-based registry that has recorded incident cases of cancer in children (0-14 years) resident in Piedmont (more than 500,000 children ages 0-14 years in 2001) since 1967. The registration is extended to residents in Piedmont diagnosed and/or treated in Piedmont as well as in other Italian regions or abroad. The sources of information include the discharge registry that keeps track of the resident population, administrative files used for reimbursement purposes, cancer death rosters, and also active search. The procedures and criteria for inclusion in the CCRP database, follow-up, and coding of cancer types have been reported elsewhere (34). CCRP contributed data to the Automated Childhood Cancer Information System project coordinated by the IARC[4] since 1976, which guarantees high quality of registration. Most cases are microscopically confirmed. For instance, 99% of leukemia cases registered in 1975 to 2001 were cytologically confirmed, and 95% of ALL cases diagnosed since 1980 were typed immunologically (35).

We considered incident cases of ALL in children from 1 to 5 years old. The year of birth of cases' mothers was obtained from CCRP records, which include parental information obtained from demographic files. Year of birth of mothers of all children born in Piedmont in the study period were available as individual anonymous records from the Italian National Institute of Statistics for children born from 1980 to

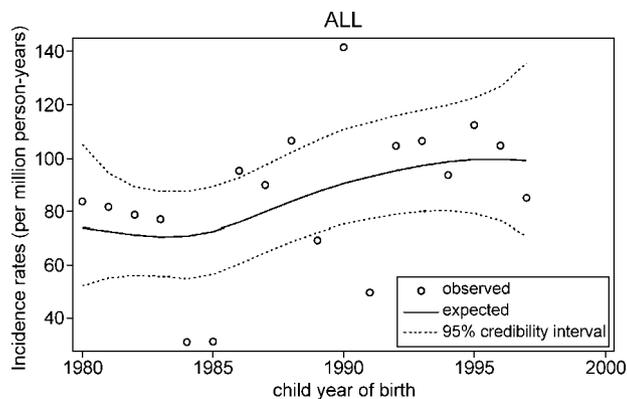[4] http://www-dep.iarc.fr/accis/data.htm

Figure 1. Observed (*dots*) and predicted incidence rates of ALL at ages 1 to 5 yr, by child year of birth. Expected values (*smooth curves*) and their 95% Bayesian credibility intervals were obtained using a generalized linear mixed model. CCRP, 1980 to 1997.

1997. Analyses were therefore restricted to this period. Analyses were further restricted to children with mothers who were 20 to 39 years old at the time of delivery, because data were too sparse outside this interval.

Statistical Analyses. We analyzed ALL incidence time trends using an age-period-cohort approach, where the period effect was represented by the child year of birth, the age effect by the age of the mother at the time of delivery, and the cohort effect by the birth cohort of the mother. We created four 4-year and one 2-year child birth cohorts (1980-1983, 1984-1987, 1988-1991, 1992-1995, 1996-1997) and six 4-year maternal age classes (20-23, 24-27, 28-31, 32-35, 36-39). Nine 8-year maternal birth cohorts were obtained by subtracting the maternal age at delivery from the child birth cohort (e.g., the maternal birth cohort of 20- to 23-year-old mothers of children born from 1980 to 1983 is 1956-1963). In this way, adjacent maternal birth cohorts overlap by 4 years.

We carried out a standard age-period-cohort analysis that includes evaluation of the drift (36-38). The term drift was used by Clayton and Schifflers (37) to denote a temporal variation of rates that does not distinguish between the influences of two of the three temporal variables involved in the analysis. For example, if both a period-cohort and an age-period model fit the data equally well, the variation over time could have a linear component in common due to either a cohort or an age effect. This component is termed drift and cannot be ascribed to either effect. To evaluate the nonlinear components of the effects of the undistinguishable variables, each of the two are introduced in the models, along with the drift.

Analyses were carried out using standard Poisson regression models available in the STATA software. Sex was considered as a potential confounder but not included in the final models because it did not change estimates by much.

A nonparametric generalized linear mixed model with a second-order autoregressive error component was used to estimate incidence time trends by calendar year of birth (39, 40) and was implemented with WinBugs (41).

Results

We observed 252 cases of ALL. As observed in previous incidence studies based on CCRP data (39), incidence rates of ALL increased over the study period (Fig. 1). The observed number of ALL cases and the corresponding incidence rates by child birth cohort and maternal age are reported in Table 1.

Table 2 summarizes the results of a formal age-period cohort analysis, in which partial age-period-cohort models of increasing complexity are evaluated. We found a linear effect of the maternal components, as the model including the drift (maternal age or maternal birth cohort linear effect) and the child birth cohort fitted the data better than the model including the child birth cohort only ($P = 0.012$; model 3 versus model 2 in Table 2). Indeed, inclusion of the drift in the model adequately described the observed rates, with no further improvement after inclusion of the child birth cohort ($P = 0.169$; model 3 versus model 4 in Table 2). We did not find evidence of nonlinear effects of maternal age or maternal birth cohort as there was no improvement in the models when the nonlinear components of maternal age or maternal year of birth were introduced (models 5 and 6 versus model 3 in Table 2).

Because the effect of the maternal characteristics was linear, as indicated by the role played by the drift, it was not possible to distinguish between the effects of maternal age and of maternal year of birth. Therefore, we modeled the observed incidence rates of ALL using the two partial models: (*a*) maternal age–child birth cohort; (*b*) maternal birth cohort–child birth cohort. Using the first partial model, we estimated the relative risks of ALL associated with maternal age (Fig. 2). Similarly, using the second model (maternal birth cohort–child birth cohort), we estimated the relative risks of ALL associated with maternal year of birth (Fig. 3). We found that the risk of ALL increased with maternal age or, analogously, decreased with increasing maternal year of birth.

The estimated annual percentage changes in incidence of ALL, estimated using different partial age-period-cohort models, are reported in Table 3. A crude estimate of 2.49% decreased to 1.83% when maternal age was taken into account, and increased to 5.72% when the confounding effect of maternal birth cohort was accommodated.

The analyses were repeated on pre–B-cell subtypes (common ALL), which decreased the sample size from 252 to 219 cases. The resulting pattern was substantially unchanged. The crude estimated annual percentage change estimate was 2.53% [95% confidence interval (95% CI), −0.03-5.16]; it decreased to 1.88% (95% CI, −0.71-4.54), including maternal age, and increased to 5.76% (95% CI, 2.07-9.57), including maternal birth cohort.

Table 1. Number of cases of childhood ALL (1-5 yr) and corresponding incidence rates by child birth cohort and maternal age (CCRP, 1980-1997)

Maternal age	Child birth cohort: No. of cases (rate per 10^6 person-years)				
	1980-83	1984-87	1988-91	1992-95	1996-97
20-23	11 (66.0)	7 (57.5)	3 (34.6)	5 (82.5)	0 (0)
24-27	14 (62.4)	11 (53.8)	13 (65.6)	15 (89.9)	8 (113.1)
28-31	17 (97.2)	14 (80.1)	22 (111.2)	22 (98.8)	13 (112.5)
32-35	11 (113.9)	5 (52.0)	14 (122.0)	22 (159.0)	9 (107.0)
36-39	3 (84.4)	2 (49.8)	7 (155.5)	3 (56.0)	1 (30.5)

NOTE: As an example, framed cells indicate incidence rates for the maternal birth cohort 1956 to 1963.

Table 2. Comparison between possible partial age-period-cohort models to fit incidence data of ALL at ages 1 to 5 yr (CCRP 1980-1997)

Model	Variables	Comparison	P*
1	Constant only		
2	Child birth cohort	2 vs 1	0.084
3	Child birth cohort, drift [†]	3 vs 2	0.012
4	Drift	3 vs 4	0.169
5	Child birth cohort, maternal age	5 vs 3	0.122
6	Child birth cohort, maternal birth cohort	6 vs 3	0.639

*P value obtained from a likelihood ratio test.
[†]Drift denotes the linear component of the temporal variation of rates due to the effect of maternal age or maternal birth cohort, with no possibility of distinguishing between the two.

Discussion

We found that incidence time trends of ALL in children 1 to 5 years old increase with both the child birth cohort and the age of the mother at the time of delivery, and decrease with the mother's year of birth.

Childhood ALL occurs most commonly in the first few years of life, with a typical peak around an age of 3 years. Due to its early onset, exposure to potential environmental risk factors is likely to occur *in utero* and may be partly related to the lifestyle of the mother during the pregnancy. This is, in turn, influenced by the calendar period in which the pregnancy occurred (period effect, in our analysis, represented by the child birth cohort) and also by the age of the mother during pregnancy and her birth cohort.

Published results on the effect of maternal age have been inconsistent even when the studies refer to largely overlapping (in space and time) data sets. Of three case-control studies on childhood leukemia conducted in California, one found a positive association with maternal age and two found no association (16-18). Shaw et al. (17) analyzed 255 children diagnosed with leukemia from 1975 to 1980, and found no association. Reynolds et al. (16), in a study based on 1,957 cases diagnosed in 1988 to 1997, found that ALL risk was elevated for children (ages 0-5 years) born to mothers >35 years old (odds ratio, 1.25; 95% CI, 1.04-1.52). Finally, Ma et al. (18), in a recent study based on 366 children (0-14 years old) diagnosed in 1995 to 2002, found no association with parental age. Also, no clear pattern emerged from six studies on childhood leukemia and maternal age in the Nordic countries (10, 12-14, 19, 32). Zack et al. (32) and Cnattingius et al. (19) reported no association in two case-control studies on children born in
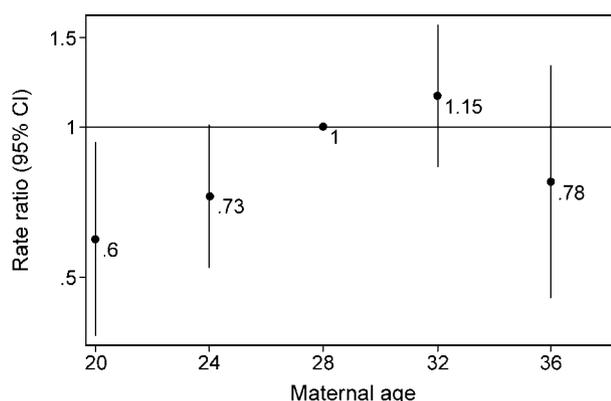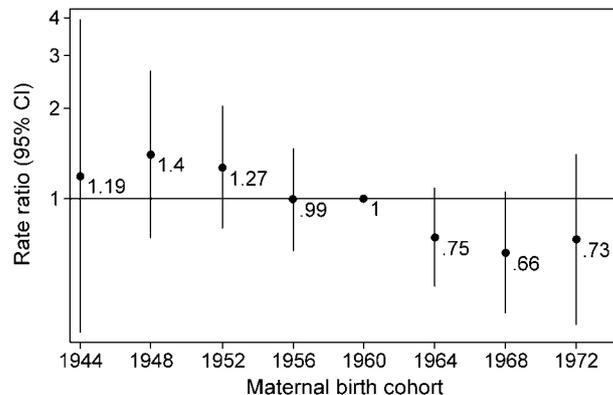
Figure 3. Rate ratios for maternal birth cohort (reference group 1960 cohort), with corresponding 95% CIs, estimated using a maternal birth cohort–child birth cohort model. Maternal birth cohorts are denoted by the middle year. CCRP, Italy, 1980 to 1997.

Sweden in the period from 1973 to 1984 (411 leukemia cases) and 1973 to 1989 (613 ALL cases), respectively. Westergaard et al. (12) analyzed a cohort of approximately 2 million children (704 ALL cases) in Denmark diagnosed in 1968 to 1992, and found that ALL risk tended to increase with increasing parental age (rate ratio for ALL in children ages 0-4 years with mothers of 30-34 years versus 20-24 years was 1.34; 95% CI, 0.99-1.80). Hemminki et al. (13) found that maternal age over 35 years conveys an excess risk of childhood leukemia of ∼50%. Results were based on a Swedish cohort, in which roughly 1,500 children ages 0 to 14 years and born after 1940 had an ALL diagnosed in the period 1960 to 1994. Another Swedish cohort of nearly 250,000 children born in 1955 to 1990 and followed up until 1994 (213 ALL cases) showed that older maternal age (>35 years) is associated with an increased risk of ALL in the early age group (0-4 years; standardized incidence ratio, 2.0; 95% CI, 1.16-3.20; ref. 14). Finally, Hjalgrim et al. (10) analyzed a case-control study based in Denmark, Sweden, Norway, and Iceland, with 1,905 ALL cases diagnosed in 1984 to 1999, and found no association with parental age.

In general, older studies found a positive association (21), whereas the most recent and largest studies did not (10, 20, 30), with one exception (16). For unknown reasons, cohort studies found an effect of older maternal age (12-15), whereas case-control studies tended to find weak or no associations (10, 16-33). Although biases might involve case-control and cohort studies to a different extent, various sources of selection or information biases do not seem to readily explain this difference. Case-control and cohort studies, however, showed some differences in the study periods considered. For instance, in Sweden, cohorts included cases diagnosed from the 1960s (13, 14), whereas case-control studies included more recently diagnosed cases, starting from the early 1970s (19, 32).

In our study, the standard age-period-cohort method of analysis was applied in a novel way, mixing temporal variables of children with leukemia and of their mothers. The most relevant limitations of our work were the small number of cases and the absence of information on potential confounders or effect modifiers (such as birth order, birth weight, and exposure to infections). Given the complexity of age-period-cohort models, we did not investigate the role of paternal age, which is highly collinear with maternal age. The few studies that considered the association of paternal age and childhood leukemia yielded inconclusive results (13, 15, 24). CCRP data did not allow to disentangle the effects of maternal age and maternal birth cohort because we found that the best-fitting model included the effect of maternal characteristics as linear (drift). We also found that inclusion of the child birth

Figure 2. Rate ratios for maternal age (reference group 28-31 yr) with corresponding 95% CIs, estimated using a maternal age–child birth cohort model. Maternal age classes are denoted by the first year. CCRP, 1980 to 1997.

Table 3. Annual percentage change in incidence of ALL at ages 1 to 5 yr by child birth cohort, estimated using different partial age-period-cohort models (CCRP 1980-1997)

	Annual percentage change by child birth cohort					
	Crude		Adjusted for maternal age*		Adjusted for maternal birth cohort*	
	EAPC	95% CI	EAPC	95% CI	EAPC	95% CI
ALL	2.49%	0.09-4.93	1.83%	−0.59-4.31	5.72%	2.29-9.27

Abbreviation: EAPC, estimated annual percentage change.
*Maternal age and maternal birth cohort introduced as continuous variables.

cohort in the model did not improve the fit; that is, the maternal time-related variables seemed to be sufficient to describe the time variation of incidence rates. However, we decided to include the child birth cohort in our selected model to maintain direct information on the diseased child and to compare with other studies. Mean maternal age in the population of Piedmont increased from 26.8 years among children born in 1980 to 30.1 years among children born in 1997, with an average annual percentage change of around 20% (Italian National Institute of Statistics). Maternal age at the time of delivery could affect the risk of cancer in offspring in many ways. Aging is associated to higher mutation frequencies and decreasing DNA repair activity. Also, some chromosomal aberrations increase with age, such as trisomy 21. Aging also changes physiologic variables and hormonal patterns, which might affect the embryonal environment (13). On the other hand, maternal birth cohort may play a role in determining the types of exposures experienced by the fetus. Diet, smoking habits, and drug use are suggested risk factors for the child, which are associated with the mother birth cohort (19, 33, 42-44).

In conclusion, because adjustment for maternal age decreased the trend estimate, whereas adjustment for maternal birth cohort increased it, clarifying the function of maternal age or birth cohort is crucial to interpret variations in temporal trends of childhood cancer. If the maternal effect were entirely due to the mother's age, the apparent increase in ALL incidence would be partly explained by the advance in maternal age. On the other hand, if the maternal effect were entirely due to the mother's birth cohort, the apparent increase of ALL incidence over time would be underestimated because it is inversely confounded by the mother birth cohort effect. However, the effects of maternal age and birth cohort are not necessarily mutually exclusive and their influences on ALL incidence trends might counterbalance to a certain extent. Analysis of longer time series and geographically heterogeneous records should enable the discernment between the effects of maternal age and birth cohort and provide both insight on the actual scenario of childhood cancer behavior in time and clues on the etiologic mechanisms linking mother characteristics to children affected by cancer.

Acknowledgments

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